PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

X16324

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

23 NOV 2005 / 23 DEC 2005

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/005198	17.02.2005	23.02.2004

International Patent Classification (IPC) or both national classification and IPC
C07K16/18, A61K39/395, A61P25/28, C12N15/13

Applicant
ELI LILLY AND COMPANY

1. This opinion contains indications relating to the following items:

- ☒ Box No I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No VII Certain defects in the international application
- ☐ Box No VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/005198

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing.

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8,10-15
	No:	Claims	1-7,9
Inventive step (IS)	Yes:	Claims	10,11,14,15
	No:	Claims	1-9,12,13
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/46237 A (NEURALAB LIMITED) 13 June 2002
D2: YOO E M ET AL: "Myeloma expression systems" JOURNAL OF IMMUNOLOGICAL METHODS, vol. 261, no. 1-2, pages 1-20, 1 March 2002

1. Novelty

The subject-matter of claims 1-7 and 9 is not new in the sense of **Article 33(2) PCT** because of the disclosures made by D1:

The document **D1** discloses a composition suitable for administration to a human subject comprising an anti-Aβ antibody that has acceptably low levels of Aβ peptide. The antibodies are humanized, preferably produced in CHO cells, myeloma cell lines or hybridomas and highly purified by standard procedures including HPLC (D1: p44, l11-l15, p45, l12-l19, p49, l22 - p51, l28). In D1, the level of contaminating Aβ peptide is not specifically examined, however, many purification methods, and in particular HPLC, can be expected to result in an undetectable concentration of the Aβ peptide.

Additionally, the specific degree of purity referred to in the claims is not considered as constituting a feature capable of imparting novelty to a known compound because conventional methods of purification, for example HPLC, yield substantially pure, even if small, quantities of the purified product.

Thus, the disclosures made by D1 anticipate the novelty of present claims 1-7 and 9.

2. Inventive step

The subject-matter of claims 8, 12 and 13 does not involve an inventive step in the sense of **Article 33(3) PCT** for the following reason:

i. The document **D1** is regarded as being the closest prior art to the subject-matter of claim 8 because it discloses a process for preparing anti-Aβ antibody suitable for therapeutic use by expression in CHO cells, myeloma cell lines or hybridomas.

ii. The subject-matter of claim 8 differs from this known process in that a specific type of myeloma cell, NS0, is used.

iii. The problem to be solved by the present invention may therefore be regarded as the identification of alternative cells for the production of anti-Aβ antibody suitable for therapeutic use.

iv. The solution proposed in claim 8 of the present application cannot be considered as involving an inventive step because NS0 cells were known in the art as useful for the production of therapeutic antibodies (see document **D2**). The selection of NS0 cells is therefore merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. A lack of inventive step is also stressed by the fact, that NS0 cells do not require any specific interference in order to avoid contamination with Aβ peptide (see example 3 of present application).

v. In the light of example 3 of the present application, it appears that NS0 cells lack the amyloid precursor protein. Thus, no specific measures have to be taken in order to obtain anti-Aβ antibody which is not contaminated by Aβ peptide. Therefore, a process for preparing anti-Aβ antibody in a cell line which lacks amyloid precursor protein is not considered inventive either.

vi. Subject-matter relating to the process for preparing the anti-Aβ antibody which comprises expression of the antibody in the presence of an inhibitor of β- or γ-secretase appears novel and inventive.